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The impact of cardiac dysfunction on acute respiratory distress syndrome and mortality in mechanically ventilated patients with severe sepsis and septic shock: an observational study

Brian M. Fuller, MD, MSCI,

Department of Anesthesiology, Division of Critical Care, Division of Emergency Medicine,
Washington University School of Medicine in St. Louis

Nicholas M. Mohr, MD,

Department of Emergency Medicine, Department of Anesthesiology, Division of Critical Care, Roy
J. and Lucille A. Carver College of Medicine, University of Iowa

Thomas J. Graetz, MD,

Department of Anesthesiology, Division of Critical Care, Division of Cardiothoracic
Anesthesiology, Washington University School of Medicine in St. Louis

Isaac P. Lynch, MD,

Department of Anesthesiology, Division of Critical Care, Division of Cardiothoracic
Anesthesiology, Washington University School of Medicine in St. Louis

Matthew Dettmer, MD,

Division of Emergency Medicine, Washington University School of Medicine in St. Louis

Kevin Cullison, MD,

Division of Emergency Medicine, Washington University School of Medicine in St. Louis

Talia Coney,

Saint Louis University School of Medicine

Swetha Gogineni, and

Saint Louis University School of Medicine

Robert Gregory

Southern Illinois University School of Medicine

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Corresponding Author: Brian M. Fuller, MD, MSCI, 660 South Euclid Avenue, Campus Box 8072, St. Louis, MO 63110, Fax: 314.3620419, Telephone: 314.7475368, fullerb@wusm.wustl.edu.

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Introduction

Sepsis and acute respiratory distress syndrome (ARDS) are two critical care syndromes that share several features. Both are common, highly lethal, and negatively impact survivors dramatically [1–5]. Intense investigation into both syndromes has resulted in little success in randomized controlled trials as well [6, 7]. Sepsis carries an estimated incidence of ARDS of over 40% in some studies and is a leading cause of death in ARDS [8–10]. Finally, the clinical care and trajectory set forth at the most proximate time of presentation [e.g. the emergency department (ED) and early intensive care unit (ICU)] are now recognized as increasingly impactful time periods with respect to overall outcome [11, 12].

Cardiac dysfunction is a prominent feature of sepsis, with an incidence as high as 60% [13]. Sepsis-associated cardiac dysfunction has been described for decades [14, 15]. Though the characterization and pathophysiology remains incompletely understood, it typically is described as involving biventricular dysfunction, decreased ejection fraction, and ventricular dilation (e.g. increased end-diastolic volume index), which is reversible in survivors over the course of 7 to 10 days [14, 16–20]. Earlier studies showed a seemingly paradoxical association with decreased cardiac function and survival, though more recent data questions this association [13, 14, 21–23]. While sepsis-associated cardiac dysfunction has not definitively been linked with worse outcome, critically ill mechanically ventilated patients (including those with ARDS) have worse outcome associated with nonpulmonary organ failure, including cardiovascular dysfunction [17, 23–26]. It is possible that cardiac dysfunction may carry a more deleterious impact in sepsis patients that are mechanically ventilated, and those with ARDS, but this has not been extensively investigated.

There is increasing interest in optimizing the care of mechanically ventilated patients early in the course of respiratory failure. This includes preventing and mitigating the severity of ARDS after ICU admission [27–29]. The event rate for ARDS after admission from the ED ranges from 6.2% to 44% [12, 30]. Recent data suggests that close to 9% of mechanically ventilated patients have ARDS while in the ED, and around 30% of mechanically ventilated ED patients with severe sepsis will progress to ARDS [31–33]. However, some of these data excluded potential ARDS patients on the assumption of left atrial hypertension in the presence of an elevated B-type natriuretic peptide (BNP), or history of heart failure or depressed left ventricular (LV) function on echocardiogram [31, 32]. As the new Berlin definition recognizes that cardiac failure and left atrial hypertension can coexist with ARDS and is more inclusionary in the definition of ARDS with respect to the origin of pulmonary edema, it is possible that cardiac dysfunction is a modifiable factor that influences both ARDS incidence and outcome, yet this remains unknown [34].

This study was therefore performed with two objectives: 1) to assess the impact of sepsis-associated cardiac dysfunction on the incidence and outcome of ARDS; and 2) to assess the impact of sepsis-associated cardiac dysfunction on mortality in mechanically ventilated patients with severe sepsis admitted from the ED. We hypothesized that the presence of cardiac dysfunction would be associated with progression to ARDS, would worsen outcome in ARDS patients, and be associated with higher mortality.

Methods

This observational study is reported in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies [35]. Financial support for this project was provided in part from the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Number UL1 TR000448. The funding organization played no role in the study concept, design, data analysis, or writing of the manuscript.

Study design

This was a retrospective observational cohort study and a preplanned secondary analysis of 251 patients previously reported [31]. This study was approved by the Human Research Protection Office at the principal investigator's (PI) institution with waiver of informed consent.

Study setting and population

This study was conducted at a university-affiliated, urban teaching hospital (1,250 beds), with an annual ED census of > 95,000 patients. Over a 5-year period [June 2005-May 2010], all mechanically ventilated patients enrolled in a severe sepsis registry were eligible for inclusion. Criteria for inclusion in the registry included: suspected infection with a lactate level ≥ 4 mmol/L, or systolic blood pressure ≤ 90 mmHg after initial fluid bolus. Patients in whom an echocardiogram was not obtained were excluded from the analysis, as were patients experiencing ARDS while in the ED.

Study protocol

Patients with severe sepsis or septic shock were identified as receiving mechanical ventilation in the ED by registry query and verified by review of the medical record. Baseline patient characteristics, lengths of stay (LOS), treatment variables, and outcome variables were collected from the electronic medical record. All data was collected by abstractors blinded to both clinical outcomes and study hypotheses. To ensure uniform data collection and accuracy, all variables were defined prior to data extraction and placed in a standardized format during the data collection process. Regular meetings and monitoring of data collection were performed. Upon completion of data collection, two other (separate) data abstractors verified all records for accuracy and cross-checked all data with electronic medical records. For the echocardiographic portion of this study, the electronic medical record was queried for the presence of a transthoracic echocardiogram for each patient within 24 hours after admission from the hospital. All echocardiograms were reviewed *post hoc* by two trained Intensivists certified in perioperative echocardiography, and each was blinded to all patient clinical information, outcome data, and study hypotheses. Echocardiographic images reviewed included parasternal long axis, parasternal short axis, apical four chamber, and apical two chamber. An adequate study was defined as adequate images from at least two views that an echocardiography reviewer deemed sufficient to determine *qualitative* function, as has been previously described [36]. Disagreement

between reviewers was resolved with via discussion and consensus between echocardiogram reviewers and the PI.

Measurements and key outcome measures

ARDS was defined according to the Berlin definition [34]. These criteria include: 1) bilateral opacities on chest radiograph or computed tomography scan not fully explained by effusions, lobar/lung collapse, or nodules; 2) respiratory failure not fully explained by cardiac failure or fluid overload; and 3) hypoxemia with a partial pressure of oxygen to fraction of inspired oxygen ratio ($P_aO_2:F_iO_2$) ≥ 300 with ≥ 5 cm H_2O positive end-expiratory pressure. In patients without an arterial blood gas measurement, the oxygenation criteria was determined by using the pulse oximeter: fraction of inspired oxygen ($S_pO_2:F_iO_2$) ratio as previously described [37]. The presence of two consecutive radiographic and oxygenation criteria was also required for ARDS diagnosis. When more than one value was present, the worst value was selected. Severe sepsis and septic shock were defined as previously described [38, 39]. The baseline patient characteristics, ventilator variables, and process of care variables have been previously described [31].

All patients with at least one echocardiogram were analyzed for qualitative characterization of cardiac function. Sepsis-associated cardiac dysfunction was defined as an estimated LV ejection fraction (EF) of $< 45\%$, as has been previously described in sepsis [13]. In patients with a previous echocardiogram showing a baseline LV EF $< 45\%$, if the current echocardiogram demonstrated a further decline in EF, this was assumed to be sepsis-associated cardiac dysfunction. In patients with a previous echocardiogram showing an LV EF $> 45\%$, if the current LV EF was $< 45\%$ it was assumed to be sepsis-associated cardiac dysfunction. RV dysfunction was defined as RV enlargement and the presence of paradoxical septal motion, as has been previously described [40, 41]. The primary outcome of interest was the impact of cardiac dysfunction on the incidence of ARDS after ICU admission. An *a priori* subgroup analysis included clinical outcomes in ARDS patients with cardiac dysfunction versus no cardiac dysfunction. A secondary outcome included the impact of sepsis-associated cardiac dysfunction on mortality.

Data analysis

Descriptive statistics, including mean [standard deviation (SD)], median [interquartile range (IQR)], and frequency distributions were used to assess the characteristics of the patient cohort. To assess the effect of cardiac dysfunction on outcome, continuous and categorical variables were compared using an unpaired t-test, Wilcoxon's test, Chi-square test, or Fisher's exact test, as appropriate. Variables with less than 10% missing data and statistically significant in univariable analyses at a $p \leq 0.10$ level were candidates for inclusion in a bidirectional stepwise, multivariable logistic regression analysis. The stepwise regression method selected variables for inclusion or exclusion from the model in a sequential fashion based on the significance level of 0.10 for entry and 0.10 for removal. Collinearity was assessed, and the model used variables that contributed information that was statistically independent of the other variables in the model. Adjusted odds ratios (aORs) and corresponding 95% CIs are reported for variables in the multivariable model, adjusted for all variables in the model. For categorical predictors, the absence of the

condition is the reference category for the aORs. For continuous predictors, aORs reflect the increased odds of the outcome for a one-unit increase in the predictor variable. The degree to which the adjusted logistic regression model fit the data was evaluated using goodness-of-fit statistics.

Results

A total of 251 patients with severe sepsis or septic shock were mechanically ventilated during the study, and 122 patients were assessed for the primary and secondary outcomes of interest (Figure 1). Table 1 shows the baseline characteristics of the study population, process of care variables, and echocardiographic findings of the cohort. Independent review of the echocardiograms yielded a kappa value of 0.60, indicating moderate agreement. After consensus discussion, there was perfect agreement between the independent reviewers and the PI. The median ejection fraction was 50.0% (35.0-60.0) in the entire cohort. Sepsis-associated cardiac dysfunction was present in 44 patients (36.1%). Table 1 also shows the risk factors for progression to ARDS after univariable analysis. With respect to baseline characteristics, unadjusted analysis showed that a higher body mass index (BMI) was associated with progression to ARDS (28.7 vs. 25.7, $p = 0.04$). No ED process of care variables were associated with ARDS. Sepsis-associated cardiac dysfunction was not associated with progression to ARDS ($p = 0.59$), nor was any other echocardiographic parameter (Figure 2). Including measured covariates significant at a $p \leq 0.10$, multivariable logistic regression analysis demonstrated that a higher BMI was associated with progression to ARDS (adjusted OR 11.84, 95% CI 1.24 to 113.0, $p = 0.02$).

In the *a priori* subgroup of patients with ARDS, cardiac dysfunction was assessed for impact on change in organ function, need for renal replacement therapy, duration of mechanical ventilation and vasopressor therapy, hospital LOS, and mortality (Table 2). Cardiac dysfunction was not associated with any of these clinical outcomes in this subgroup of patients with ARDS. Table 3 shows the predictor variables for the secondary outcome of interest, mortality. Unadjusted analysis showed that sepsis-associated cardiac dysfunction was also not predictive of mortality. The following variables were candidates for inclusion in the multivariable model (Table 4): vasopressor use, SOFA score, age, lactate, and APACHE II. Cirrhosis ($n = 3$) and central venous pressure [CVP ($n = 67$)] were not candidates for the final model due to the small numbers of patients with these parameters. After multivariable logistic regression analysis, age was the only significant predictor of mortality (aOR 0.96, (5% CI 0.93, 0.99, p -value 0.02).

Discussion

Since no treatment targeting the underlying pathophysiology of ARDS exists, assessing modifiable patient characteristics or treatment variables is vital to prevent and mitigate the severity of the syndrome. This study targeted a patient cohort that was both septic and mechanically ventilated, two factors placing them at high risk for potentially worse outcomes associated with cardiovascular dysfunction. We first sought to determine the influence of cardiac dysfunction on the incidence of ARDS. In our cohort of mechanically ventilated patients with severe sepsis and septic shock, 46.7% of patients progressed to

ARDS. This is a similar rate to previous investigations into sepsis as an ARDS risk factor, and further highlights the need to target ARDS preventive strategies in these patients [9, 42–45]. Increased alveolar permeability and edema is a pathophysiological underpinning of ARDS, and an increase in edema-promoting (Starling) forces can worsen pulmonary function and contribute to worse outcome in these patients[46]. As such, depression in LV function has greater potential to contribute to the development of ARDS in at-risk patients with increased alveolar epithelial-capillary endothelial permeability. However, we did not see an association with sepsis-associated cardiac dysfunction and progression to ARDS in this study. Several possible explanations exist. We only sought to assess cardiac function on a qualitative basis, as this reflects the most common clinical practice in the ICU and ED setting [47, 48]. It is therefore possible that while sepsis-associated cardiac dysfunction was present in 36.1% of the patients, increased hydrostatic pressure was not present. Without directly measuring left atrial pressure, or assessing for elevated filling pressures with doppler echocardiography, that question is difficult to answer. It is also possible that with such a high event rate for ARDS in this cohort, cardiac dysfunction and hydrostatic edema plays a relatively smaller role in ARDS development when compared to the high permeability (e.g. oncotic) edema that accompanies septic shock. In the current investigation, a higher BMI was associated with progression to ARDS. This has been demonstrated in several studies before, and likely represents a combination of factors, including higher baseline inflammation associated with obesity and altered respiratory system mechanics [31, 49–52].

Nonpulmonary organ failure is associated with worse outcome in mechanically ventilated patients [26]. Furthermore, several investigations have shown that nonpulmonary organ failure is a prime determinant of outcome in ARDS [53–56]. Given these facts, we hypothesized that cardiac dysfunction would be associated with worse clinical outcomes in this high risk subgroup of patients. Cardiac dysfunction was not associated with pulmonary and non-pulmonary organ dysfunction, hospital length of stay, or mortality in patients with ARDS. This outcome may be driven by the small number of patients (n= 57) in this subgroup analysis, or related to how sepsis-associated cardiac dysfunction was defined in this study. It is possible that other echocardiographic parameters could be predictive. As sepsis-associated cardiac dysfunction is typically reversible over the first week of illness, it is also possible that it does not affect overall outcome. Previous investigations into the impact of cardiac dysfunction on mortality in sepsis have resulted in conflicting data. Earlier studies showed an association between biventricular dysfunction and dilation and survival; this was not reproduced by much of the more recent data [14, 21, 23, 57]. This further highlights the need to better standardize the definition of sepsis-associated cardiac dysfunction, and study its impact on outcome in a prospective fashion [17].

Limitations

There are several important limitations to this study. The retrospective design limits ability to draw causation on any effect of cardiac dysfunction on ARDS incidence. However, we excluded patients with ARDS while in the ED (n= 9), suggesting a temporal relationship would have existed between early cardiac dysfunction and subsequent ARDS development. The retrospective design may have influenced the event rate for cardiac dysfunction as well.

Prospective data collection, with uniform timing of echocardiography may have changed our results, as treatment variables received (e.g. fluids and vasopressors) can alter the loading conditions of the heart, filling pressures, and influence cardiac function. So it is possible that the assessment of cardiac function would have been different, but our early process of care variables were similar between the ARDS versus no ARDS groups. Furthermore, the method by which cardiac dysfunction in sepsis has been defined and characterized has changed over the years, and is yet to be standardized [17]. Given this fact, the working definition used in this study and event rate obtained (36.1%) are likely valid. The echocardiographic images were also reviewed *post hoc* and the interpretation of the images could have been different if assessed on a real-time, prospective basis. However, the images reviewed would have been similar, and all images were reviewed in a blinded fashion, providing some assurance that the methodology of assessing cardiac function was appropriate. We also did not exclude patients with pre-existing cardiac disease, as some previous studies have [23]. This may have increased our false positive rate for sepsis-associated cardiac dysfunction (i.e. type I error), yet excluding these patients would not inform on real world clinical scenarios and limit generalizability. The definition of ARDS has also changed since the study subjects were cared for clinically. This could have impacted clinical care at the time of treatment and outcomes. This is also a relatively small study. However, a sample size of 122 patients is larger than the majority of studies examining sepsis-associated cardiac dysfunction [23].

Conclusions

In mechanically ventilated patients with severe sepsis and septic shock, progression to ARDS and cardiac dysfunction are common. Cardiac dysfunction was not associated with outcome across our cohort of patients, nor in the subgroup of patients with ARDS. Further investigation, with adequately powered prospective studies, should be undertaken, as it is possible that cardiac dysfunction could be a modifiable factor in the prevention and treatment of ARDS.

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Highlights

- The impact of sepsis-associated cardiac dysfunction on ARDS was examined
- 36.1% of mechanically ventilated septic patients had cardiac dysfunction
- A higher BMI was associated with progression to ARDS
- Cardiac dysfunction had no impact on ARDS or mortality

Figure 1.

Flow diagram depicting the patients analyzed to achieve each objective of the study. ARDS: acute respiratory distress syndrome; ED: emergency department.

Figure 2.
demonstrates no association between the incidence of ARDS and ejection fraction.

Table 1

Baseline characteristics and univariate risk factors for progression to ARDS

	Entire Cohort (n=122)	Progression to ARDS (n=57)	No progression to ARDS (n=65)	p [#]
Baseline characteristics				
Age (years)	63.0 (51.2 – 77.0)	64.9 (16.5)	61.4 (15.2)	0.22
Male, n (%)	61 (50.0)	27 (47.4)	34 (52.3)	0.59
Comorbidities, n(%)	36 (29.5)	13 (22.8)	23 (35.4)	0.13
Diabetes	3 (2.5)	3 (5.3)	0 (0)	0.10
Cirrhosis	20 (16.4)	10 (17.5)	10 (15.4)	0.75
Malignancy	23 (18.9)	8 (14.0)	15 (23.1)	0.20
COPD				
Height (in)	66.6 (4.3)	66.5 (4.9)	66.6 (3.6)	0.95
Weight (kg)	78.3 (61.3–90.9)	82.5 (60.0–93.2)	76.3 (62.8–86.4)	0.14
IBW (kg)	63.0 (11.0)	62.9 (12.1)	63.0 (10.0)	0.95
BMI	26.5 (22.4–31.1)	28.7 (22.9–34.1)	25.7 (21.8–29.9)	0.04
Lactate	3.3 (1.8–5.7)	3.2 (1.8–5.9)	3.6 (1.9–5.4)	0.79
Troponin	0.3 (0.1–1.6)	0.4 (0.1–2.3)	0.3 (0.1–1.2)	0.66
BNP	365.0 (138.0–1134.0)	262.0 (111.5–527.0)	842.0 (169.0–2004)	0.09
APACHE II *	23.7 (6.2)	24.2 (5.7)	23.3 (6.7)	0.41
SOFA *	8.9 (3.4)	9.2 (3.5)	8.6 (3.3)	0.39
CVP (n= 67)	12.0 (9.0–18.0)	12.0 (10.0–19.0)	12.0 (7.5–17.5)	0.40
S _{cv} O ₂ (n= 57)	77.0 (69.0–83.0)	77.0 (70.0–84.0)	77.0 (66.0–82.0)	0.76
ED LOS	5.5 (4.2–7.6)	5.6 (4.4–7.1)	5.3 (4.0–7.7)	0.72
Process of Care variables				
Fluids over first 6 hours (liters)	3.0 (2.0–4.0)	3.3 (2.0–4.0)	3.0 (2.0–4.0)	0.74
Vasopressor use, n (%)	96 (78.7)	45 (79.0)	51 (78.5)	0.95
Blood product administration, n (%)	11 (9.0)	4 (7.0)	7 (10.8)	0.47
S _{cv} O ₂ monitored, n (%)	57 (46.7)	27 (47.4)	30 (46.2)	0.89
S _{cv} O ₂ 70 % achieved, n (%) **	44 (77.2)	21 (36.8)	25 (35.4)	0.89
Echocardiographic findings				
Cardiac dysfunction present, n (%)	51 (41.8)	22 (38.6)	29 (44.6)	0.50
Sepsis-associated cardiac dysfunction, n (%)	44 (36.1)	22 (38.6)	22 (33.8)	0.59
RV dysfunction, n (%)	47 (38.5)	21 (36.8)	26 (40.0)	0.72
Biventricular dysfunction, n (%)	26 (21.3)	9 (15.8)	17 (26.2)	0.16
Ejection fraction (%)	50.0 (35.0–60.0)	50.0 (40.0–60.0)	50.0 (35.0–55.0)	0.51

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; IBW: ideal body weight; BMI: body mass index; BNP: B-type natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment Score; CVP: central venous pressure; S_{cv}O₂ central venous oxygen saturation; ED: emergency department; LOS: length of stay; RV: right ventricle

Continuous variables are reported as mean (standard deviation) and median (interquartile range).

p-value comparison of progression to ARDS versus no ARDS

* Modified score, which excludes Glasgow Coma Scale

** Refers to the 57 patients with S_{cVO_2} monitored while in the ED.

Table 2

The impact of cardiac dysfunction on clinical outcomes in the subgroup of patients with ARDS (n= 57)

Outcome	Cardiac dysfunction (n= 22)	No cardiac dysfunction (n= 35)	<i>p</i>
SOFA	−4.0 (−4.0 —1.0)	−3.0 (−4.0 —2.0)	0.73
Dialysis, n (%)	6 (27.3)	8 (22.9)	0.71
Mechanical ventilation duration (hours)	154.0 (98.5–308.6)	147.3 (82.8–263.7)	0.54
Vasopressor duration (hours)	88.3 (13.2–111.2)	57.8 (32.7–143.2)	0.76
HLOS (days)	13.0 (5.0–18.0)	13.0 (7.0–20.0))	0.44
Mortality, n (%)	12 (54.6)	18 (51.4)	0.82

ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment Score; HLOS: hospital length of stay

Continuous variables are reported as median (interquartile range).

refers to the change in SOFA score from ED baseline to 24 hours

Table 3

Univariate comparison of risk factors for mortality

	Mortality (n= 48)	No mortality (n= 74)	<i>p</i>
Baseline characteristics			
Age (years)	65.2 (16.2)	60.2 (15.6)	0.09
Male, n (%)	24 (50)	37 (50)	1.0
Comorbidities, n(%)			
Diabetes	15 (31.3)	21 (28.4)	0.73
Cirrhosis	3 (6.3)	0 (0)	0.06
Malignancy	11 (22.9)	9 (12.2)	0.12
COPD	8 (16.7)	15 (20.3)	0.62
Height (in)	66.9 (4.9)	66.3 (3.8)	0.42
Weight (kg)	77.4 (59.2–92.8)	79.5 (62.8–90.9)	0.99
IBW (kg)	64.0 (11.9)	62.3 (10.4)	0.39
BMI	25.3 (21.4–32.8)	27.4 (22.6–30.2)	0.85
Lactate	3.5 (2.4–7.2)	3.1 (1.8–4.5)	0.05
Troponin	0.3 (0.1–1.6)	0.3 (0.1–1.6)	0.81
BNP	398 (99.5–1189)	365 (148–1134)	0.94
APACHE II *	26.4 (6.6)	22.0 (5.4)	<0.001
SOFA *	10.1 (3.1)	8.1 (3.3)	0.001
CVP, n= 67	10.5 (8.0–12.5)	13.0 (10.0–19.0)	0.02
ScvO ₂ , n=57	78.0 (72.0–84.0)	77.0 (65.0–82.0)	0.38
ED LOS	5.5 (4.1–6.9)	5.7 (4.3–7.7)	0.41
Process of Care Variables			
Fluids over first 6 hours (liters)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.28
Vasopressor use, n (%)	42 (87.5)	54 (73.0)	0.06
Blood product administration, n (%)	5 (10.4)	6 (8.1)	0.75
ScvO ₂ monitored, n (%)	20 (41.7)	37 (50)	0.37
ScvO ₂ 70% achieved, n (%) **	19 (33.3)	25 (43.9)	0.04
Echocardiographic findings			
Cardiac dysfunction present, n (%)	19 (39.6)	32 (43.2)	0.69
Sepsis-associated cardiac dysfunction, n (%)	16 (33.3)	28 (37.8)	0.61
RV dysfunction, n (%)	17 (35.4)	30 (40.5)	0.57
Biventricular dysfunction, n (%)	9 (18.8)	17 (23.0)	0.58
Ejection fraction (%)	55.0 (35.0–60.0)	50.0 (35.0–55.0)	0.51

COPD: chronic obstructive pulmonary disease; IBW: ideal body weight; BMI: body mass index; BNP: B-type natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment Score; CVP: central venous pressure; ScvO₂: central venous oxygen saturation; ED: emergency department; LOS: length of stay; RV: right ventricle

Continuous variables are reported as mean (standard deviation) and median (interquartile range).

* Modified score, which excludes Glasgow Coma Scale

** Refers to the 57 patients with ScvO₂ monitored while in the ED.

Stepwise multivariable logistic regression model of variables and adjusted odds ratio for death for subgroup of 107 patients with data for all variables.

Table 4

Variable	adjusted OR [#]	95% CI for aOR	ENTRY INTO MODEL		REMOVAL FROM MODEL	
			Incremental r ² (selection order) [†]	p-value	Incremental r ² (step for removal) [†]	p-value
Vasopressor use	NS					
SOFA *	NI		0.14 (1)	0.0009	0.21 (4)	0.19
Age	0.96	0.93, 0.99	0.23 (3)	0.02		
Lactate	NS					
APACHE II *	1.14	1.06, 1.23	0.17 (2)	0.08		

SOFA: Sequential Organ Failure Assessment Score; APACHE: Acute Physiology and Chronic Health Evaluation

* Modified score, which excludes Glasgow Coma Scale

CI = confidence interval; aORs=adjusted odds ratios; NS = not significant in the stepwise procedure; NI = not included in the final stepwise model.

[#] aORs reflect the increased odds of death for a 1-unit increase in the variable.

[†] Rescaled generalized coefficient of determination of the fitted model.